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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/203,500	12/01/98	HONOLD K	P564-8025

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SANDALS,W	
ART UNIT	**PAPER NUMBER**
1636	16

DATE MAILED: 07/17/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/203,500	Applicant(s) Honold et al.
	Examiner WILLIAM SANDALS	Group Art Unit 1636

☒ Responsive to communication(s) filed on *May 11, 2000*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *20-43* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *20-43* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Continued Prosecution Application

1. The request filed on May 11, 2000 in Paper No. 15 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/203,500 is acceptable and a CPA has been established. An action on the CPA follows.

Response to Arguments

2. Arguments set forth in Paper No. 11, filed April 3, 2000 have been considered regarding the rejection of claims 20-28, 30-36 and 39 under 35 USC 102 and found persuasive. The rejection is withdrawn.

3. Amendment of claim 35 in Paper No. 11 have overcome the rejection of the claim under 35 USC 112, second paragraph, and the rejection is withdrawn.

4. Arguments set forth in Paper No. 11 regarding the rejection of claims 20-43 under 35 USC 103 have been considered but are not found convincing. The rejection makes obvious the invention because all of the elements cited in the rejection are obvious to use to make the invention. The '977 patent teaches "changing the expression of a nucleic acid sequence which is present endogenously in a eukaryotic cell". The rejection of the claims clearly sets forth a motivation to combine the references. The rejection is repeated below along with responses to the arguments set forth in Paper No. 11.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 20-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat. No. 5,695,977 in view of WO97/37012, WO94/12650 and Cruz et al.

The claims are drawn to a process of changing the expression of a nucleic acid sequence which is endogenously in a eukaryotic cell by transfecting the cell with a vector which encodes a marker gene, and possibly a second marker gene, which may be a negative selection marker gene, and a gene of interest operably linked to an expression control sequence flanked by recombinase sites which may be *lox* sites, which is flanked by sequences for homologous recombination, and where the encoded gene(s) of interest is expressed. The gene of interest may be DHFR. DHFR may be amplified once it is introduced into the cell. Further claimed is a Hif binding sequence which is a gene expression control sequence, and where the gene DHFR is targeted by homologous recombination (ie, the homologous flanking sequences are from the DHFR gene) for inactivation in the transfected cell.

US Pat No. 5,695,977 taught (see especially columns 1, 2 and 4-8) a process of changing the expression of a nucleic acid sequence which is endogenously in a eukaryotic cell by

transfecting the cell with a vector which encodes a marker gene, and possibly a second marker gene, which may be a negative selection marker gene, and a gene of interest operably linked to an expression control sequence flanked by recombinase sites which may be *lox* sites, which is flanked by sequences for homologous recombination, and where the encoded gene(s) of interest is expressed. The gene of interest may be DHFR. DHFR may be amplified once it is introduced into the cell.

US Pat. No. 5,695,977 did not teach a Hif binding sequence which is a gene expression control sequence, and where the gene DHFR is targeted by homologous recombination (ie, the homologous flanking sequences are from the DHFR gene) for inactivation in the transfected cell.

WO97/37012 taught (see especially the abstract, the summary, the claims, the Figures and pages 12-22) a process for changing the expression of a nucleic acid sequence which is present endogenously in a eukaryotic cell by transfecting the cell with a vector which comprises a gene and/or a positive selective marker gene flanked by recombinase site-specific sequences, which are flanked by sequences for homologous recombination. The recombinase site-specific sequences may be LoxP sequences. A negative selection marker may be located outside the homologous recombination sequences. The nucleic acid located between the recombinase site-specific sequences may be excised by a transient activation of a site-specific recombinase. The expression control sequence may be a hypoxia-induced nucleic acid sequence (see page 12, lines 1-2).

WO94/12650 (see especially the abstract, the summary, the Figures the claims and pages 9-13, 17-19 and 21-23) taught the insertion by homologous recombination of an expression controlling nucleic acid element into the genome of a cell adjacent to a gene of interest, where the construct encoded a gene for DHFR where DHFR may be amplified.

Cruz et al. taught (see the entire article) the insertion of a construct into a host genome where the homologous flanking sequences were DHFR sequences, creating a host cell which was DHFR-negative.

It would have been obvious to one of ordinary skill in the art when the instant invention was made to modify the teachings of US Pat. No. 5,695,977 with WO97/37012, WO94/12650 and Cruz et al. to produce a process for changing the expression of a nucleic acid sequence which is present endogenously in a eukaryotic cell (which cell may be a human cell) by transfecting the cell with a vector which comprises an expression control sequence and a gene and/or a positive selection marker gene flanked by recombinase site-specific sequences, which are flanked by sequences for homologous recombination where the recombinase site-specific sequences may be LoxP sequences and where a negative selection marker may be located outside the homologous recombination sequences and where the nucleic acid located between the recombinase site-specific sequences may be excised by a transient activation of a site-specific recombinase with the homologous recombination vector of WO 97/37012 and the homologous recombination vector of WO 94/12650, and the homologous recombination vector of Cruz et al. because US Pat No. 5,695,977 taught the advantageous use of homologous recombination vectors to introduce

genes of interest which may be flanked by recombinase sites such as *lox* which are in turn flanked by homologous recombination sites. Use of a homologous recombination vector for the specific limitations such as producing DHFR negative cells with a vector which has DHFR flanking homologous sequences to target the insertion of the construct/vector into the genome of a host cell, and the introduction of an expression control sequence such as HIF-binding nucleic acid sequences adjacent to an endogenous gene in the host genome were all well known techniques for gene manipulation in a host cell, as taught by US Pat. No. 5,695,977, WO97/37012, WO94/12650 and Cruz et al. Further, WO97/37012 taught the introduction of a hypoxia induced expression control sequence into a region of a desired gene in a host genome and Cruz et al. taught the application of DHFR to the introduction of a construct for controlling expression into a host cell and a host cell genome.

One of ordinary skill in the art would have been motivated at the time the instant invention was made, to modify the teachings of US Pat. No. 5,695,977 with WO97/37012, WO94/12650 and Cruz et al. because limitations such as using DHFR negative cells with a DHFR encoding vector, and DHFR flanking homologous sequences to target the insertion of the construct/vector into the genome of a host cell, and the introduction of an expression control sequence such as HIF-binding nucleic acid sequences adjacent to an endogenous gene in the host genome were all well known techniques for gene manipulation in a host cell, as taught by US Pat. No. 5,695,977, WO97/37012, WO94/12650 and Cruz et al. WO97/37012 taught the introduction of a hypoxia induced expression control sequence into a region of a desired gene in

a host genome as did Mazure et al. Cruz et al. and WO94/12650 taught the application of DHFR to the introduction of a construct for controlling expression into a host cell and a host cell genome. Studies of host genomes by manipulation of DHFR genes such as employed in the instant claimed invention are taught in Cruz et al. at page 173, columns 1 and 2 which show the advantages of integrating vector DNA into the host genome at DHFR loci, and also where the host cells are DHFR defective. At page 11, lines 19 bridging to page 12, line 2 WO97/37012 states "[t]he promoter may regulate the expression of a gene constitutively, or differentially with respect to the tissue in which expression occurs or , with respect to the developmental stage at which expression occurs, or in response to external stimuli such as physiological stresses...such as those induced by anaerobiosis or hypoxia". One of skill in the art would therefore be motivated to combine the teachings of US Pat. No. 5,695,977 with WO97/37012, WO94/12650 and Cruz et al. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of US Pat. No. 5,695,977 with WO97/37012, WO94/12650 and Cruz et al. It was therefore prima facie obvious to combine the teachings of US Pat. No. 5,695,977 with WO97/37012, WO94/12650 and Cruz et al. at the time the instant invention was made to produce the instant claimed invention. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of US Pat. No. 5,695,977 with WO97/37012, WO94/12650 and Cruz et al.

7. ***Response to Arguments***

8. Arguments in Paper No. 9, filed October 15, 1999 assert that the US Pat. No. 5,695,977 is a hodgepodge of the same limitations as the instant invention, and that the elements are not set forth in the order set forth in the instant invention. The order of the limitations does not alter the case, since US Pat. No. 5,695,977 sets forth the limitations and allows for the user to set any order which may make the use of the invention in a manner suited to the situation. US Pat. No. 5,695,977 sets forth the homologous recombination vector which has all of the embodied limitations as set forth in the rejection above.

Each of WO97/37012, WO94/12650 and Cruz et al. taught specific embodiments of the invention, which in combination with the primary reference make the instant invention obvious. Motivation to combine is given above.

In response to applicant's arguments in Paper No. 9 against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

9. In response to applicant's argument in Paper No. 11 that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the

knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the WO '012 patent and Cruz et al. are relied upon to teach the well known elements of a vector construct as stated in the motivation statement in the rejection.

10. Cruz et al. taught the equivalence and general utility of the method in the discussion at page 173 that "[o]verall, the features of linear DNA transfection in *Leishmania* are similar to those reported for *S. cerevisiae*".

11. In response to applicant's arguments in Paper No. 11 against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

12. In response to applicant's argument in Paper No. 11 that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Conclusion

13. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.
Examiner
July 15, 2000

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER